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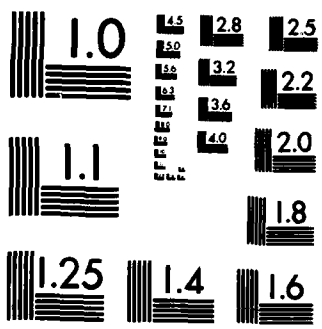

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Circadian Rhythms
Phase-Resetting of Circadian Pacemakers
Pharmacological Therapy
Mathematical Modeling.
Sleep-Wake Cycles
Jet-Lag
Squirrel Monkey

ABSTRACT (Continue on reverse side if necessary and identify by block number)

This research program concerned the physiological mechanisms that underlie the phenomenon of jet-lag and aimed ~~to develop~~ therapeutic techniques to minimize the performance and physiological deficits that occur in rapid transmeridian air travel. During the course of this project, the circadian pacemaker responsible for the timing of the daily rest-activity was identified in the brain of the diurnal primate, the squirrel monkey (Saimiri sciureus).

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The suprachiasmatic nuclei were also identified in the human brain. A number of other significant advances included: developing a model of the circadian sleep-wake cycle, characterizing how phase shifts of the light-dark cycle reset the timing of the sleep-wake cycle, and identifying pharmacological agents which can phase-reset the circadian system.

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DEPARTMENT OF THE AIR FORCE

GRANT AFOSR 78-3560

JET-LAG PREVENTION:

PHYSIOLOGICAL MECHANISMS AND PHARMACOLOGICAL THERAPY

FINAL SCIENTIFIC REPORT

APRIL 1, 1973 - MARCH 31, 1983

Submitted By: Martin C. Moore-Ede, M.D., Ph.D.

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I. RESEARCH OBJECTIVES

The symptoms of "jet-lag" are suffered by Air Force personnel as well as the millions of civilians who travel across time zones. Jet-lag is characterized by deteriorations in performance, malaise, inability to concentrate, and other physiological and psychological symptoms. A similar syndrome is suffered by ground crews who work on shift work schedules as well as combat forces who must function "around the clock." Until recently little has been known about the mechanisms of jet-lag and there have been no very effective methods of prevention.

This research program aimed to define the anatomical and physiological nature of the circadian pacemakers which timed the approximately 24-hour sleep-wake cycle and to develop safe and practical methods that would be useful in minimizing jet-lag in man. Certain pharmaceutical compounds have been shown in lower organisms to be effective in resetting biological clocks. These offer the exciting possibility of resynchronizing "body time" to any time zone shift, and hence alleviating the problems of jet-lag. The research program is examining the efficacy of these compounds using a diurnal primate, the squirrel monkey, which has a circadian (approximately 24 hour) sleep-wake cycle that is very similar to that in man.

Specific Aims

1. Development of a diurnal primate model with a relatively consolidated circadian sleep-wake cycle
2. Determination of the three-dimensional architecture of the primate suprachiasmatic nucleus (SCN) (one of the key circadian pacemakers)
3. Identification of the SCN in the human brain
4. Investigate two-pacemaker organization of the primate circadian timing system
5. Examine the coupling between the body temperature rhythm and rest-activity cycle
6. Analyze the mechanisms of phase-resetting by light
7. Determine the characteristics of the resetting of the sleep-wake cycle after light-dark cycle phase shifts
8. Investigate the effectiveness of potential pharmacological phase-resetting agents

II. RESEARCH ACCOMPLISHMENTS

A number of major advances were made in the understanding of the structure and function of the circadian pacemakers in human and non-human primates during the course of this research program supported by the AFOSR. These are summarized below.

A) Development of a diurnal primate model with a consolidated sleep-wake cycle

Virtually all of the work on neural control of the mammalian circadian timing system, with the exception of that from our laboratory, has been conducted in nocturnal rodents. Similarly, much of the work on the regulation of sleep in mammals has been conducted in either nocturnal rodents or in cats, species which do not have the consolidated sleep-wake cycle seen in man. There are major problems in investigating phase-resetting agents in such species because they have both fundamentally different temporal relationships to the environmental light-dark cycle (i.e., nocturnal vs. diurnal), and have relatively weak circadian organization of sleep so the animal's behavior consists of naps throughout day and night rather than uninterrupted sleep during the night and uninterrupted wakefulness during the day as is seen in humans.

A major accomplishment of this laboratory has been to develop an animal model with a sleep-wake cycle (as well as other rhythms) that is much more similar to that of humans than species so far studied. We have demonstrated that the diurnal squirrel monkey (Saimiri sciureus) shows a sleep-wake cycle that has consolidated sleep during the night and protracted wakefulness during the day. By using a chronically-implanted headpiece, a swivel commutator system and electrophysiological recording equipment, we have developed a capability to continuously monitor the sleep-wake cycle, body temperature rhythm, and other circadian functions for months at a time under controlled environmental conditions in isolation chambers. We demonstrated a highly consolidated sleep-wake cycle under light-dark conditions and, furthermore, a gradual resynchronization of the sleep-wake cycle after a phase advance of 6 hours in the timing of the light-dark cycle. The free-running circadian rhythm of sleep and wakefulness in the squirrel monkey was found to be approximately 25 hours--a value that is very similar to that of human subjects.

B) Determination of the complex three-dimensional architecture of the primate SCN

Because little information was available on the anatomy of the suprachiasmatic nuclei in primates, one of the first efforts undertaken was to define the structure of this pacemaker. A three-dimensional computer reconstruction of the SCN was undertaken digitalizing tracings of successive histological sections of the hypothalamus and then analyzing them using advanced computer graphics.

The striking feature of the primate SCN in 3-D was its complex morphology. The anterior poles of each nucleus have a broad medial to lateral expanse ranging up to 0.8 mm. The posterior poles of the nuclei appear to be rotated 90° with respect to the plane in which the anterior poles lie

oriented. The posterior poles also appear to extend dorsally rather than laterally.

An important result of these studies was the demonstration of the anatomical relations of the optic recess (the anterior tip of the third ventricle) to the SCN. This information has subsequently enabled the development of techniques to apply pharmacological agents to the vicinity of this pacemaker.

C) Identification of the SCN in the human brain

The use of studies of the squirrel monkey as a model of the human circadian system depends on there being a close homology between the species. However, the very existence of the SCN in man has been seriously questioned in a number of authoritative works on the hypothalamus.

We, therefore, set out to examine the neuroanatomy of the human hypothalamus to see if an SCN could be identified. Using the Yakovlev Library collection of human and primate brains at the Armed Forces Institute of Pathology in Washington, D.C., comparisons of the brains of New World and Old World primates and human fetal, child, and adult brains were made. These revealed a cluster of neurons in the human brain that seemed to be homologous to the non-human primate SCN. Phylogenetic changes in the dimensions of the third ventricle, however, mean that the apparently homologous cluster of neurons is more laterally placed in human brains than in non-human primates. Furthermore, the neuronal cluster is more diffusely organized in humans than in lower species, particularly rodents and New World primates.

A comprehensive study of the literature revealed that damage to this area was associated with a disruption of the human sleep-wake cycle. Tumors which damage the anterior tip of the third ventricle and optic chiasm (the location of the SCN) can cause sleep disorders, so that patients repeatedly fall asleep at any hour of the day (like SCN-lesioned animals). Thus, the human SCN would appear to serve a similar function to that of primates.

D) Demonstration of two-pacemaker organization of the primate circadian timing system

A number of simultaneous experimental approaches including reanalysis of data from human subjects, mathematical modeling of the circadian system, and neurophysiological experiments in squirrel monkeys led us to the conclusion that the circadian timing system in primates is best characterized as two major pacemaking systems which preside over a large population of secondary oscillators. This argument was developed in full in 1982 in a book which Dr. Moore-Ede (with Dr. Sulzman and Dr. Fuller) co-authored entitled, The Clocks That Time Us: Physiology of the Circadian Timing System, which was published by Harvard University Press, and is also summarized in a recent Federation Proceedings review (Moore-Ede, 1983). Firstly, the data from human subjects indicate that the circadian rhythms in human subjects in environments without time cues fall into two classes which can, on occasion, internally desynchronize and free-run with separate periods. REM sleep propensity, plasma cortisol concentration and urinary potassium excretion maintain a continuing temporal relationship with the core body temperature

rhythm during internal desynchronization. In comparison, the rhythms of skin temperature, plasma growth hormone concentration and urinary calcium excretion tend to follow the rest-activity cycle and the circadian timing of slow wave sleep. We have labeled the pacemaker driving the core body temperature and its group of correlated variables as X, and the pacemaker driving the second group which includes the rest-activity cycle as Y. Normally these two pacemakers are mutually coupled so they maintain synchrony with each other and with environmental time cues. The identity of X and Y pacemakers are indicated by studies involving lesions of the suprachiasmatic nuclei; after such lesions the body temperature (Fuller et al., 1981) and the plasma cortisol rhythm (Reppert et al., 1982) persist while there is extensive disruption of the rest-activity, feeding and drinking rhythms. This leads to the conclusion that the SCN may be the Y pacemaker driving certain behavioral rhythms, whereas the X pacemaker is located outside the SCN in a separate anatomical location. In addition to these two pacemakers, there appear to be multiple other secondary oscillators in the organism because, even after total destruction of the SCN, it takes some time for the organization of the activity rhythm to become arrhythmic. Complex ultradian patterns develop which eventually dissipate, suggesting that the secondary oscillators can generate some damped rhythmicity.

E) Desynchronization between the body temperature rhythm and the rest-activity cycle

An important advance was made by the demonstration that the body temperature and rest-activity rhythms of squirrel monkeys can be forced to simultaneously exhibit different periods, and to pass through a full 360° of relative phase. Five adult male squirrel monkeys have now been exposed to a cycle of 14 hours of darkness (LD 14:14) for a minimum of 21 days. (Three animals have experienced the protocol twice.) In this regime, the rest-activity rhythm entrained to the 28-hour zeitgeber period in 7-8 cases; however, the temperature rhythm failed to entrain in 5 of the 6 cases for which data were complete. The temperature rhythm in these 5 cases exhibited a period around 26 hours so that approximately every 13 days the two rhythms passed through every possible phase relationship with respect to each other.

This was the first demonstration of desynchronization from other than human subjects. It suggests that the circadian timing system in intact squirrel monkeys contains a minimum of two pacemakers which are capable of at least partially independent function. Further analyses of the data from desynchronized animals should enable estimation of parameter values for a mathematical model of the squirrel monkey system, as a basis for comparison with the two-oscillator model for the human circadian timing system (Kronauer et al., 1982) on which this laboratory continues to collaborate.

F) Mechanisms of phase-resetting by light

The environmental light-dark cycle acts as a major circadian synchronizer in all mammalian species, including non-human primates and man. However, the mechanisms of entrainment, while well characterized in nocturnal rodents, had not been determined in primates. A number of important questions, therefore, have arisen as to whether the mechanisms of entrainment described for such nocturnal animals were applicable for diurnal species such as most non-human primates and man.

To study the mechanisms of entrainment, a phase-response curve was generated for the squirrel monkey utilizing three-hour pulses of light (600 lux) presented to 6 individually housed animals, free-running in constant darkness. Phase delays occur in early subjective night and phase advances in late subjective night with minimal phase-resetting in the middle of subjective day. This pattern is similar to that of nocturnal rodents. The relative weighting of phase advances and phase delays during the subjective day suggests that the normal light-dark cycle falls both on phase advance and phase delay portions of the curve, but the net result is an advance. This is as would be predicted from this species which has a mean free-running period of approximately 25 hours and must be reset on average by a daily phase advance of one hour.

G) Resetting of the sleep-wake cycle in the squirrel monkey after environmental phase shifts

To validate the squirrel monkey as a model for the regulation of the human sleep-wake cycle, monkeys were subjected to 8-hour light-dark cycle phase shifts in both the advance and delay directions in a cross-over design. The phase advance was enacted by shortening of the photoperiod, and the delay by extension of the photoperiod. Temperature, locomotor activity and sleep-wake states were recorded continuously 24 hours a day for two baseline days and then for two weeks after the phase shifts.

The data revealed a large and consistent asymmetry in resynchronization times, with adjustment to phase advances requiring more than twice as long (7-8 days) as phase delays (2-3 days) to complete. This is comparable to the asymmetry seen in man. During the transient cycles, sleep state structure and temporal placement were disturbed. In addition to being a powerful synchronizer of the system, light, particularly at onset, appeared to have pronounced evoked or direct effects on sleep/wake behavior and body temperature.

Analyses of phase-tracking cosinor methods, local mean-level crossings and sleep stage accumulation times indicate the comparability of the regulation of the sleep-wake cycle in the squirrel monkey and in man.

H) Preliminary studies on phase-resetting agents

During the last year of the funding period we developed techniques to administer pharmacologic agents to squirrel monkeys to evaluate their phase-resetting actions. As a result of these studies we found that single pulses of an antibiotic, anisomycin, in non-toxic dosages are a resetter of circadian rhythms in the squirrel monkey. Further studies will be needed to determine the efficacy of this compound.

Initial studies were also commenced looking at the efficacy of GABA-mimetic agents, including sodium valproate. These were found to have marked effects on changing the period of the circadian system. These agents have interesting implications because of the especially high levels of GABA in the SCN. Future studies will pursue these findings with the aim of developing clinically feasible techniques to facilitate adaptation after travel across time zones.

III. CUMULATIVE CHRONOLOGICAL LIST OF WRITTEN PUBLICATIONS IN TECHNICAL JOURNALS

The five-year funding period (1978-1983) resulted in two books and over 50 scientific articles and published abstracts.

1. Moore-Ede, M.C.; Sulzman, F.M.; Fuller, C.A. The Clocks That Time Us: Physiology of the Circadian Timing System. Cambridge, MA: Harvard University Press, 1982.

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13. Lydic, R.; Moore-Ede, M.C. Three dimensional structure of the suprachiasmatic nuclei in the diurnal squirrel monkey (Saimiri sciureus). Neurosci. Lett. 17: 295-299; 1980.

14. Fuller, C.A.; Sulzman, F.M.; Moore-Ede, M.C. Shift-work and the jet-lag syndrome: conflicts between environmental and body time. Johnson, L.C.; Tepas, D.I.; Colquhoun, W.P.; Colligan, M.J. eds. The Twenty-four Hour Workday. Proceedings of a Symposium on Variations in Work-Sleep Schedules. Washington, D.C.: National Institute of Occupational Safety and Health Publication No. 81-127; 1981: pp.305-320.

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23. Moore-Ede, M.C. Hypothermia: a timing disorder of circadian thermoregulatory rhythms? Pozos, R.S., Ed. The Nature and Treatment of Hypothermia. Minneapolis: University of Minnesota Press; 69-80; 1983.

24. **Albers, H.E.; Lydic, R.; Moore-Ede, M.C. Entrainment and masking of circadian drinking rhythms in primates: influence of light intensity. Physiol. Behav. 28: 205-211; 1982.**

25. **Sulzman, F.M.; Fuller, C.A.; Moore-Ede, M.C. Circadian entrainment of the squirrel monkey by extreme photoperiods: interactions between the phasic and tonic effects of light. Physiol. Behav. : ; 1982. (Submitted)**

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33. Moore-Ede, M.C.; Czeisler, C.A.; Richardson, G.S. Circadian time-keeping in health and disease. Part 2: Clinical implications of circadian [illegible]. NEJM [illegible]

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IV. LIST OF PROFESSIONAL PERSONNEL ASSOCIATED WITH THE RESEARCH EFFORT

1. Martin C. Moore-Ede, Principal Investigator
2. Dr. Frank M. Sulzman
3. Dr. H. Elliott Albers
4. Dr. Philippa Gander
5. Dr. Charles A. Czeisler
6. Mr. David B. Wexler
7. Dr. David Borsook
8. Dr. Gary Richardson

V. INTERACTIONS

Dr. Moore-Ede has had multiple interactions with scientific colleagues at professional meetings and also with various governmental offices, including the scientific meetings of the Air Force Office of Scientific Research. The other professional staff have presented papers at scientific meetings and are constantly in touch with colleagues at other universities and at governmental laboratories.

A list of scientific presentations made is included:

1. Fuller, C.A.; Sulzman, F.M.; Moore-Ede, M.C. Active and passive responces of circadian rhythms in body temperature to light-dark cycles. Fed. Proc. 37: 832; 1978. 62nd Annual Meeting FASEB 4/9-14/1978, Atlantic City, N.J.

2. Sulzman, F.M.;Fuller, C.A.; Moore-Ede, M.C. Influence of light intensity on squirrel monkey circadian rhythms. Fed. Proc. 37: 832; 1978. 22nd Annual Meeting, APSS, June 16-20, San Antonio, TX.

3. Sulzman, F.M.; Fuller, C.A.; Moore-Ede, M.C. Phasic and tonic effects of light on the primate circadian timekeeping system. Am. Soc. Photobiol. VI Annual Meeting, Burlington, Vt., 1978.

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6. Pierce, B.G.; Sulzman, F.M.; Fuller, C.A.; Moore-Ede, M.C. Light pulses reset the circadian clock in a primate. Am. Soc. Photobiol. VI Annual Meeting, Burlington, Vt., June 11-15, 1978.

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8. Moore-Ede, M.C.; Sulzman, F.M.; Fuller, C.A. Uncoupling of circadian oscillators at the limits of light-dark cycle entrainment in the squirrel monkey. Fed. Proc. 38: 1979. 63rd Annual Meeting, FASEB, April 1-10, 1979, Dallas, TX.

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